EXHIBIT 3

The effect of prewarming by a Bair Paws gown on redistribution hypothermia in patients undergoing total joint replacement or colorectal surgery

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A. General Information

List of abbreviations

GCP – Good Clinical Practice
CRF – Case Report Form
DSMB – Data Safety Monitoring Board

Trial Summary

The purpose of this trial is to determine whether the use of the Bair Paws warming system prior to the induction of anesthesia will reduce the incidence and extent of redistribution hypothermia in surgical patients

B. Background Information

Introduction

Perioperative hypothermia can produce significant postoperative morbidity and complications.[1-7] Initially, the largest contributor to intraoperative hypothermia is the redistribution of body heat caused by anesthesia-induced vasodilation. The hypothermia caused by redistribution can be significantly reduced by increasing mean body temperature through preinduction skin-surface warming or prewarming. Prewarming is an effective technique to reduce intraoperative hypothermia because it decreases the temperature gradient between the core and peripheral thermal compartments, and it has little effect on preinduction core temperature.

The Bair Paws warming system consists of a full-length hospital gown that contains an internal forced-air warming blanket. The warming unit has a single continuously-variable control that can adjust the outlet temperature between ambient and 42°C and the air flow from 4 to 6 L/s. The Bair Paws gown system has been used to provide thermal comfort to perioperative patients, but its prewarming efficacy had not been established in patients.

The effect of prewarming on core temperature before the induction of anesthesia is extremely minimal; therefore, it is generally difficult to measure the extent of prewarming by performing standard clinical thermometry prior to anesthetic induction. The thermal effect of prewarming, however, is easily detected by comparing core temperature in prewarmed and unprewarmed subjects following the induction of anesthesia.

Description of the Investigational Device or Technique

The prewarming system used in this study is comprised of the Bair Paws gown (Model 81001) and the Arizant model 875 warming unit. Both of these devices are fully released medical products that will be used according to their approved labeling.

Literature Review

Introduction

Hypothermia, or a drop in human core temperature below 36.0°C, is a common consequence of anesthesia and surgery. Most inhalational and some intravenous anesthetics act directly on the human thermoregulatory system and cause a lowering of the thermoregulatory setpoint[8, 9], a decrease in the metabolic rate[10], and a redistribution of heat from the body's core to the periphery because of the lowering of peripheral vascular resistance[11]. The sudden drop of peripheral vascular resistance produces immediate core hypothermia even though mean body temperature (MBT) changes very little[12]. Moreover, surgery further enhances heat loss by exposing large, moist body surfaces to cold surroundings. The physiological effects of surgical hypothermia include coagulopathies[2, 6, 13], attenuation of the immune response[14], arrhythmias[5], delayed drug metabolism[7], increased oxygen consumption[15], increased catecholamine release[16], and shivering[17]. These physiological effects produce several adverse clinical outcomes, including myocardial ischemia, discomfort, bleeding, increased incidence of surgical wound infections, increased time spent on mechanical ventilation, increased intensive care and hospital length of stay, and increased cost[1].

Several devices and techniques are used to augment heat gain or minimize heat loss in surgical patients. Convective warming blankets have been used successfully for about 15 years to warm

patients during surgical procedures. The few drawbacks to the use of convective warming blankets include inadequate time to deploy the systems in shorter duration cases, inaccessibility of patient skin surface area because of surgical requirements, limited effectiveness during the first hour of anesthesia, burn risks during aortic cross-clamping or in patients with poor tissue perfusion, and unwillingness to use forced air systems in ultra-clean surgeries such as orthopedic cases.

Despite the fact that man is a homeotherm and aggressively resists changes in his core temperature, several investigators have shown that prewarming certain parts of the human body prior to the induction of anesthesia is possible[18-20]. Preinduction warming, or prewarming, is defined as the transient elevation of MBT for the purpose of mitigating anesthetically-induced hypothermia. When performed correctly, prewarming alone is capable of preventing significant surgical hypothermia for up to 3 hours in suitable individuals. For whole-body prewarming, the optimal temperatures and duration have been determined[21]. While prewarming is known to improve surgical outcomes[22], the additional presurgical time needed to adequately prewarm patients has prevented its widespread adoption. The development of prewarming systems that are easy to use and require less time to raise mean body temperature should greatly improve the adoption of this technique for short duration surgeries.

Surgical duration

The trend toward shorter anesthesia control time and surgical duration has significantly reduced the amount of time that patients spend in the operating room. The motivation to reduce surgical duration derives from a desire to improve both clinical productivity rates and postsurgical outcomes, especially reductions in surgical site infections[23, 24]. The introduction of new anesthetic and surgical techniques and rapid recovery protocols allow patients to emerge from anesthesia more quickly and, in many cases, completely bypass the postanesthesia care unit[25]. Nowhere is this trend more noticeable than in outpatient surgical centers. Figure 1 illustrates the rate of outpatient surgery cases performed in the U.S., which now greatly exceeds the number of inpatient procedures[26]. In general, outpatient surgical cases are usually shorter than inpatient cases because outpatients are usually healthier and clinics have better economies of scale and are able to take advantage of improved scheduling techniques. The trend toward shorter duration surgery has important implications for warming therapy because, as will be explained later, methods for maintaining perioperative normothermia differ depending on the surgical length.

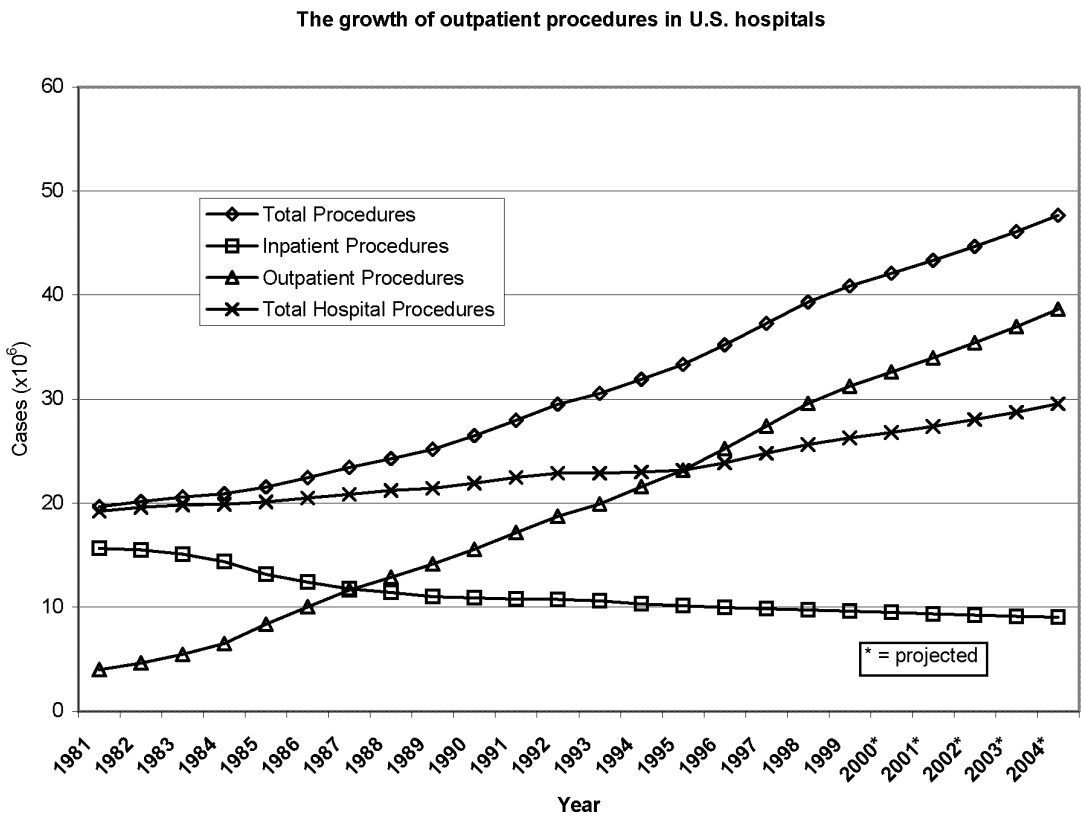

Figure 1 - Surgical procedures in the U.S. (Verispan/SMG)

Body Temperature

The human body does not have a single representative temperature because the temperatures of the various tissues of the human body vary with respect to time, topography, and ambient conditions[27, 28]. Although several multicompartment models exist that describe the human thermoregulatory system, for the purposes of this discussion, the body may be considered as consisting of two major thermal compartments: the core, which consists of the major thoracic, abdominal, and cranial organs, and the periphery, which consists of the arms, legs, and large portions of the skin[29]. The thermal setpoint of both compartments is approximately 37°C; however, the temperature of the core compartment is maintained within extraordinarily tight, short-term limits of approximately ±1.0 °C while the peripheral regions can vary as much as 5 °C without producing any ill effects[30, 31]. Under normal conditions, a spatial and temporal thermal gradient exists between the internal core and the outer skin surface, depending on the metabolic and ambient conditions. Moreover, the temperature at different regions on the body's surface also varies depending on the distance from the core, the rate of capillary blood flow at the surface, and the heat loss or gain at that site[27, 32]. The variability of body temperature in different regions makes the estimation of mean body temperature (MBT) exceedingly difficult, even under steady-state conditions, although several computational methods have been developed [33, 34].

The temperature of an object is a measure of its kinetic energy[29]. The kinetic energy of an object is the product of its mean temperature and mass. The fundamental unit of energy is the joule (J), defined as

$$1\mathrm{J} = 1\mathrm{kg} \cdot \mathrm{m}^2/\mathrm{s}^2 = 0.239 \text{ calorie}$$

The amount of kinetic energy in the human body is determined by computing the sum of the products of temperature and mass for all of the different constituent masses and temperatures in the body[29]. As there is no current way to measure temperature and mass simultaneously at all of the different locations within the body, several methods to estimate mean body temperature (MBT) have been developed. All these techniques depend on the assumptions that large areas of the external surface of the body are isothermic at steady-state conditions, that the core is relatively isothermic and massive, and that, while body mass is somewhat stratified, it remains relatively constant.

The most commonly used techniques to estimate MBT require the nearly simultaneous measurement of skin temperature at a large number of skin surface locations. The temperatures from these locations are area-weighted and summed to provide an estimate of mean surface temperature (MST). The MST is mass-weighted and summed with the mass-weighted rectal temperature to produce an estimate for MBT.

There are several limitations to the use of this technique for measuring MBT. While at first glance it would seem that more skin surface sensors might produce a better estimate for MST, an accuracy limit is reached after approximately ten sites are measured because of instrumentation errors.[35] For this reason, MST techniques that rely on six sensors are almost as accurate as those that rely on twelve sensors[36, 37]. Also, the accuracy of physical sensors, such as thermocouples and thermistors, can be variably affected by ambient conditions. Radiometers, which measure infrared radiation from a defined region and thermography, the estimation of temperature based on infrared radiation, have been used to characterize the temperature of specific regions of the body, but these methods have drawbacks, as well, including nonsimultaneity of measurement and alignment of the sensor during repeated measures of the same region[32, 38].

Another significant limitation to the estimation of MST by the representative-site method is the requirement for a relatively steady state within the representative areas. This limitation also extends to the use of rectal temperature as an estimate of core temperature. Several investigators have suggested that the esophageal and tympanic sites are more accurate during transient changes in core temperature, although pulmonary artery (PA) blood temperature and hypothalamic temperature remain the most reliable sites for measuring core temperature[39].

Heat Loss and Gain

The principle source of heat within the body is the metabolic oxidation of glucose, protein, and fat[40]. The generation of heat within the body is not homogeneous but varies spatially and temporally. At rest, the major organs, such as the brain and liver, contribute most; during exercise, however, increases in heat production may increase by a factor of ten[40]. Other usually minor sources of heat include the consumption of warm food and drink and the absorption of photons from hot surfaces and the sun.

The average basal heat production and specific heat (c_p) in a 68 kg man are approximately 80 watts and 3598 J/kg-°C, respectively[41]. The heat balance equation is

$$\dot{E}_{st} = E_{in} - E_{out} + E_q \text{, where}$$

$\dot{E}_{st}$ is the rate that energy is stored in the body,

E_{in} is the amount of energy entering the body,

E_{out} is the amount of energy leaving the body, and

E_q is the metabolic heat production.

If it were possible to completely insulate the body so that $E_{in} = E_{out} = 0$, the following equations apply:

$$\dot{E}_{st} = E_q = m \cdot c_p \frac{dT}{dt}, \text{ so}$$

$$\frac{dT}{dt} = \frac{2.9x10^5 \frac{J}{h}}{(68kg)(3598\frac{J}{kg-°C})} = 1.2°\frac{C}{h}$$

The internal temperature would rise at a rate of approximately 1.2 °C/h.

In order to maintain a thermal balance, the body must lose as much heat as is produced[29]. Heat is lost by radiation, convection, and conduction. Smaller amounts of heat are lost by evaporation and respiration. A minimally clothed person at normal room temperatures loses the majority of his heat through radiation[42].

During surgery, the metabolic rate is reduced and the radiation losses increase because significant areas of skin are exposed to an environment where the mean radiant temperature of the walls and ceiling is quite low[43]. Also, the air in the operating room is cool and is conveyed at relatively high velocities, an environment which increases the rate of convective heat loss.

Physiology of Thermoregulation

Humans are homeotherms, which means that they regulate their internal core temperature within very narrow limits of a predetermined setpoint despite relatively large internal or external perturbations[31]. The human thermoregulatory system is composed of sensory, computational, and responsive elements; the system is quite adaptable and uses a feed-forward control scheme to anticipate core temperatures based on integrated sensory information.[44]

Within the central nervous system (CNS), neurons within the hypothalamus are responsible for integrating central and cutaneous temperature data and orchestrating a response so as to maintain internal temperature within very narrow limits[45]. While the majority of neurons in the preoptic area and anterior hypothalamus are insensitive to temperature, they do appear to play a significant role in modulating the effector responses to changes in temperature. Precisely how hypothalamic cells transduce thermal information into neural signals is not yet known; however, research to date suggests that resting membrane potentials change in response to changes in local temperature[45]. Moreover, hypothalamic cells are also sensitive to nonthermal stimuli such as osmolality, glucose concentration, reproductive steroids, bacterial endotoxins, such as lipopolysaccharide, and calcitonin gene related protein (implicated as the cause of postmenopausal hot flashes)[45].

Cutaneous temperature is sensed by specialized neurons that contain thermally sensitive ion channels known as Thermal Transient Receptor Potential, or ThermoTRP channels. There are several classes of ThermoTRP channels, each of which has a specific response to a given temperature range and also to chemicals like capsicum and menthol[46]. Ultimately, thermal information is converted into a stream of action potentials, the frequency of which is determined by the membrane potential of the cutaneous thermal receptor neuron[31].

Once the CNS integrates the peripheral and central temperature data, it must determine a course of action that is likely to produce homeothermy. That is, the body must try to respond in such a way as to maintain a thermal balance between itself and the external thermal environment. The most effective way for the body to respond is through behavioral means: adding or removing clothing, moderating physical activity, moving to cooler or warmer areas, or moving into or out of the radiant energy of the sun. The ability of man to survive in the extreme cold of outer space by wearing a space suit is a behavioral adaptation that maintains a normal heat balance.

The effector response of the CNS to changes in peripheral and central temperature is adaptive and relies on a feed-forward type of control to anticipate future core temperature based on currently-sensed peripheral heat losses[44]. Under normal conditions, the gain applied to the central

temperature signal is very high and the gain applied to the peripheral temperature signal is relatively low; however, under certain rapidly changing ambient temperature conditions, the CNS may rely solely on the integrated skin temperature signal[47]. This means that under normal conditions, small central temperature changes provoke a profound effector response whereas large peripheral temperature changes provoke a relatively mild effector response. However, if the rate of temperature change in the periphery increases above some set limit, the CNS applies a much larger gain to the peripheral temperature signal so that it can actually dominate the effector response. Also, as the peripheral thermoreceptor signal dominates the proprioception of thermal comfort or discomfort for the entire body[48], the design of prewarming systems must balance the necessity for high rates of peripheral heat transfer without triggering thermal discomfort.

If behavioral responses are inadequate to maintain a heat balance, effector responses from the anterior hypothalamus stimulate the sympathetic nervous system to initiate autonomic responses to maintain an acceptable heat balance. In general, the responses are graded so as to make the most efficient use of the body's resources[48]. Examples of these responses include vasoconstriction, nonshivering thermogenesis (in infants only), metabolic rate increases, and shivering for heat gain and, for heat loss, vasodilatation, metabolic rate decreases, and sweating. Shivering and sweating are extremely effective mechanisms used by the body to maintain its temperature. Heat losses from sweating can be as high as 680 J/s for every liter[49]; heat gains from shivering can be several times the resting metabolic rate[50]. Unfortunately however, shivering and sweating have high energy costs associated with them and cannot be maintained for long periods of time because of exhaustion and hypovolemia, respectively.

During periods of homeothermy under thermoneutral conditions, the body appears to be able to maintain precise control of internal temperature by adjusting the vasomotor tone of the arteriovenous anastomoses of the hands. Several investigators have recorded very large (up to 4°C) transient temperature fluctuations in both the fingers and hands under these conditions[51].

Anesthesia and Thermoregulation

Inhalational and intravenous anesthetic agents reduce the metabolic rate and decrease the peripheral vascular resistance (PVR)[52]. Both of these physiologic alterations tend to produce hypothermia in humans because less heat is produced at the same time that more radiation surface area is recruited for heat loss. Anesthesia also prevents the body from mounting a behavioral response to the sudden loss of heat. The triple threat of anesthesia-induced heat loss leads to a profound decrease in core temperature during surgery. The decrease in PVR has one advantage: almost any external body surface is acceptable as an effective heat exchange surface during anesthesia. Under certain conditions, intraoperative warming of the legs provides adequate augmentation of heat to maintain a near normal thermal balance[53].

Several methods are used to preserve or augment body heat during surgery. Despite its relative ineffectiveness, fluid warming is used in a large number of surgical settings.[54] Among the more effective systems is forced-air warming (FAW)[55]. A FAW system consists of a warming unit and a dispersive coverlet. The warming unit heats and pressurizes a stream of filtered air that is pumped into the coverlet. The coverlet is an inflatable, two-layer blanket that has an air permeable side positioned so as to face the patient and is usually positioned on the anterior surface of the patient. Heated air is expelled from the permeable surface of the blanket so that it impinges on the skin surface. The dominant mode of heating by a FAW system is by convection; however, radiation also contributes a significant amount of heat to the subject because the temperature of the blanket surface is roughly that of the expelled air.

Several sizes and designs of FAW blankets exist. The most popular blankets are disposable and intended for single-patient use to prevent cross-contamination. All published prewarming studies to date have used full-body warming blankets.

Redistribution

Following induction with most inhalational anesthetics, the human body initially experiences an immediate decrease in core temperature without a corresponding decrease in MBT that is a result

of redistribution of heat from the core to the periphery[11]. All modern inhalational anesthetics (Isoflurane, Desflurane, Halothane, and Sevoflurane) and most modern intravenous anesthetic agents (Thiopental, Propofol, Etomidate, but not Ketamine[56]) decrease peripheral vascular resistance[52]. Even epidural anesthesia with Chloroprocaine produces significant hypothermia due to redistribution[57]. One effect of decreasing peripheral vascular resistance is the loss of vascular compartmentalization between the periphery and core sections of the body[57]. The loss of separation between the two sections allows the heat in the core to enter the periphery. Initially, redistribution results in a decrease in core temperature but no change in MBT; however, the increase in radiative, convective, and conductive losses produces an inevitable decrease in MBT and core body temperature. The redistribution is driven by the initial temperature difference between the core and the peripheral parts of the body and is responsible for approximately 65% of hypothermia during the first three hours of anesthesia[40]. Many factors influence the amount by which redistribution reduces core temperature, but the most important is the total heat content of the body just prior to anesthesia[40].

Figure 2 illustrates the characteristic three-phase decrease in core temperature following the administration of general anesthesia[58]. Each of the three phases has a dominant cause that suggests that treating each phase requires a separate approach. The initial decrease in core temperature is caused primarily by a nearly adiabatic redistribution of heat and cannot be significantly reversed by the external application of heat because the temperature difference between the warming device and the subject's skin decreases. This limitation is especially significant as operative times become shorter because once a subject becomes hypothermic due to redistribution, any method that applies external skin surface warming will be only marginally effective at raising MBT. The relative ineffectiveness of cutaneous warming during the first hour of anesthesia suggests that prewarming may be a significantly more effective method for managing hypothermia, especially for short surgical cases[20, 59]. The second phase is the result of heat losses, dominated by radiation, that exceed the metabolic rate of heat production. The second phase is the most amenable to measures to preserve core temperature by either passive or active means such as insulation and external warming. The third phase, or plateau, occurs when the heat loss and production rates are equivalent and is significantly correlated with the amount of exposed body surface area[60]. The plateau may develop passively, by limiting heat loss by skin surface warming, or occur once the patient's thermoregulatory system responds at very low core temperatures[40].

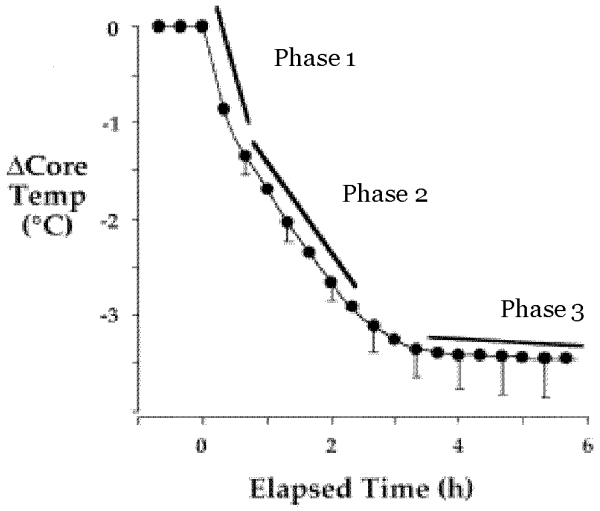

Figure 2 - Three phases of anesthetic-induced hypothermia

Because of the significant physiological differences between unanesthetized and anesthetized patients, warming strategies also differ. As discussed before, the goal of prewarming is to raise

the temperature of the peripheral parts of the body; the goal of intraoperative warming is to maintain core temperature as close to 37 °C as possible. The unanesthetized body vigorously resists attempts to raise its core temperature and is highly sensitive to the rate at which peripheral temperature increases and mildly sensitive to absolute peripheral temperature, thus placing limits on the rate and duration of any attempt at prewarming. Under normal conditions, the signal from central thermoreceptors has a higher gain than does the signal from the peripheral thermoreceptors; however, under conditions where skin temperatures change rapidly, the peripheral signal may become the sole input responsible for initiating the sweating response[47, 48]. The main reason for this behavior is that, unlike many other physiological control systems that use negative feedback, the thermoregulatory system in humans is based on a feed-forward control system[61]. From a teleological perspective, this control arrangement is the more thermodynamically efficient because it promotes behavioral management over physiologically costly metabolic or humoral responses.

Prewarming

Although homeotherms aggressively resist changes to their core temperature, several studies in humans demonstrate that under certain conditions the peripheral compartment temperature can be increased without provoking a successful compensatory response to reduce mean body temperature[21].

One paradoxical, but predictable, consequence of preinduction warming is a compensatory and transitory decrease in core temperature. The decrease in core temperature (figures 3 and 4) is caused by a redistribution of heat within the body in response to decreased peripheral heat losses and depends mainly upon the efficacy of the warming unit[62]. The rate at which core temperature decreases could be used as an assessment tool for the development of PW systems; however, this technique may have limited use due to the onset of sweating and discomfort before a measurable decrease in core temperature occurs. Another possibility for assessing the performance of prewarming systems is the magnitude of the preinduction skin-surface temperature gradient between the calf and toe. Recent studies have shown that a significant linear correlation exists between preinduction skin-surface temperature gradients and the amount of redistribution hypothermia that develops in the first postinduction hour[63].

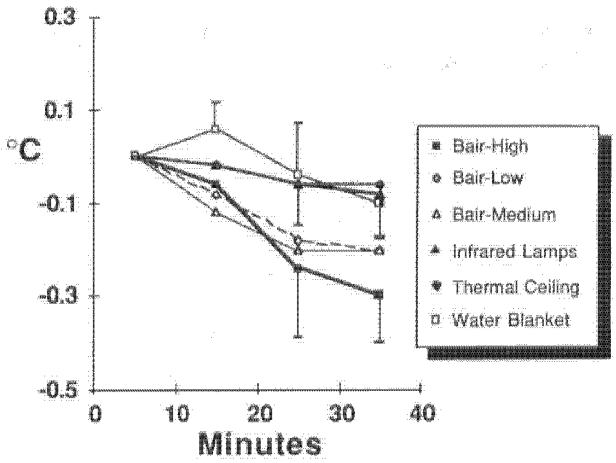

Figure 3 – Core temperature decrease during preinduction warming with several types of warming units and various temperature settings (from Sessler, DI and Moayeri, A. Anesthesiology 1990;73(2))

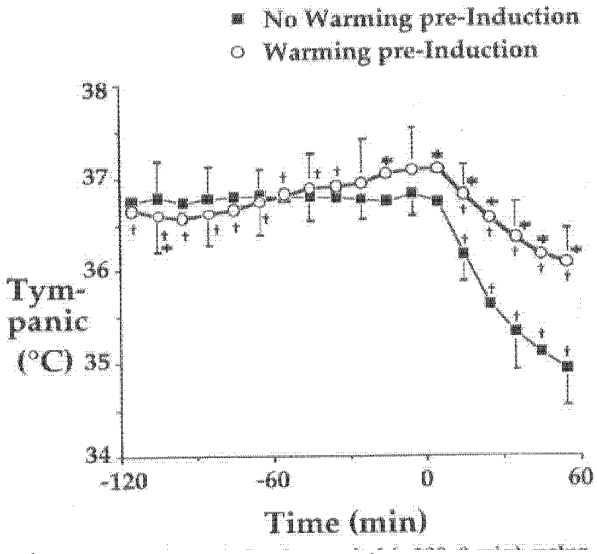

Figure 4 - Comparison of core temperatures in pre- and unwarmed volunteers before and during general anesthesia (from Sessler, DI and Moayeri, A. Anesthesiology 1990:73(2))

Although the consequences of intraoperative hypothermia have been known or suspected since the early 1970s, early attempts at prewarming with the existing circulating water mattress technology did not produce good results. The water mattress was placed beneath the patient so that the warming surface of the mattress made contact with the posterior surface of the patient. The failure of these devices to produce adequate levels of prewarming or even intraoperative warming was attributed to the poor matching of the mattress to an adequate amount of skin surface or to the possibility that tissue forces were so great in the areas of contact that the blood flow was occluded[64]. Prewarming human subjects has been performed using full-body, forced-air, convective warming blankets, which have been shown to be significantly more effective than conductive or radiative warming mattresses[55, 62, 65, 66]. This warming technique is limited only by the initiation of sweating in the subject. Once sweating begins, it is impossible to add any more energy to the subject by convective heat transfer because the energy lost by the phase change of sweat is much greater than that which can be added by convection[21].

Following the introduction of the forced-air warming blanket in the late 1980s, several investigators began to experiment with full-body blankets as a way to prevent redistribution hypothermia. As a prelude to these studies, the thermal capacity of the peripheral thermal compartment was measured in normal adult volunteers by measuring the heat flux in ten, area-weighted surfaces and summing that with the metabolic heat produced during periods of hypothermic rewarming[62]. Depending on the temperature change observed within the peripheral compartment, heat storage values ranging from 335 to 1600 kJ have been observed, although a value of 600 kJ is typical for an approximately 1.8°C temperature change[67, 68]. As expected, the thermal storage capacity is strongly correlated to body surface area and mass.

Trials involving volunteer subjects have shown that prewarming can be tolerated for up to two hours if the warming temperature is approximately 35°C[19]. In a comparison of heat loss rates in nude volunteers undergoing general anesthesia with Isoflurane, 45 minutes of prewarming at a mean blanket temperature of about 37°C, which imparts approximately 270 kJ into the subject's body with a forced air convection blanket, was shown to have little effect on the preinduction core temperature (37.3 ±0.3°C vs. 36.8 ±0.2°C) compared to unwarmed controls but significantly increased length of time that the prewarmed subjects remained normothermic[18]. Also, after thirty minutes of nude exposure in a cool operating room, the prewarmed subjects were approximately

0.8°C warmer than their matched controls, even though the heat loss rates in the prewarmed subjects were always much greater in the warmed than in the unwarmed control subjects. The greater heat loss rates in the warmer subjects are the result of radiation heat transfer losses that are driven by the absolute mean radiant temperature differences between the subject and his surroundings.

Hypothermia is also a common sequela of neuraxial anesthesia. A cross-over study of volunteers undergoing epidural anesthesia with 1.5% lidocaine demonstrated that prewarming for two hours at a relatively low temperature (38°C) was able to halve the temperature drop in subjects assigned to the warming arm[69]. Prior to anesthetic induction, the mean skin temperature of the warmed subjects was approximately 4.6°C warmer than the unwarmed subjects; however, there was no statistically significant difference between the core temperatures[19].

The demonstration that preinduction warming prevented redistribution hypothermia in volunteers suggested that it would work in patients under more pragmatic conditions and for more lengthy surgeries. A randomized control trial of hip arthroplasty patients demonstrated that prewarming the anterior skin surface for approximately 90 minutes using radiation heat transfer (an electric mattress with a surface temperature of 43°C) was able to maintain normothermic conditions for major orthopedic surgeries that lasted about three hours[70]. The fact that core temperatures began to increase after about 90 minutes of warming suggests that the electric warming pads were able to replace more heat energy than that lost during surgery and anesthesia. Another advantage of using radiant heat transfer is that the patients could continue to be warmed even after they began to sweat, as there was little chance of forced evaporation from convection. Despite the fact that all of the prewarmed subjects in this study began to sweat after about 60 minutes of prewarming, all subjects reported feeling comfortable or indifferent during the exposure to the warming mattress.

Prewarming has been shown to reduce the incidence of postoperative surgical wound infections by a significant amount in a large, randomized control study. Clean surgery (breast, hernia, varicose vein) patients who received thirty minutes of corporeal prewarming had significantly lower surgical site infections and consumed significantly less postoperative antibiotics than did their control cohorts[71].

Another pragmatic study performed in short duration surgeries in an outpatient setting using FAW demonstrated that prewarmed patients remained significantly warmer than their control cohorts and had significantly greater levels of postoperative thermal comfort[72].

As the addition of prewarming therapy increases the amount of time that must be scheduled to complete a surgery, the cost implications of prewarming therapy are of great interest to OR managers. Since intraoperative warming techniques become increasingly effective following the first hour of anesthesia, it is important to determine the least amount of prewarming time that provides effective protection from hypothermia within the first hour. The speed with which convective rewarming may be conducted depends on the following factors: 1) the maximum tolerable skin temperature, 2) surface area, and 3) sweating.

The maximum safe skin temperature in humans is approximately 41°C; sustained temperatures above 41°C will cause thermal injury to intact skin[73, 74]. Skin temperatures below 41°C may also produce thermal injury in poorly perfused skin or in tissues that are compressed, such as those below a bony prominence[75]. Because heat energy must be transferred at the highest safe temperature to reduce the time necessary to prewarm, the key to minimizing prewarming time is the recruitment of sufficient body surface area to participate in heat exchange. Volunteer studies have shown that corporeal prewarming can impart approximately 290 kJ in the first thirty minutes and 419 kJ in the first hour to the arms and legs.[21]

Sweating can significantly limit the effectiveness of prewarming by forced-air convection because even at relatively high air temperatures, the rate at which heat is lost by sweating is much greater than the capacity of any convective warmer to overcome. Devices that impart heat where the

dominant mode of heat transfer is radiation are not subject to this limitation. Also, as discussed previously, as the onset of sweating is mediated by the sum of neural signals representing MBT and the rate of cutaneous temperature change, careful titration of energy transfer by any means can prevent the onset of sweating. Also, the exclusion of certain areas from prewarming therapy, such as the hands, feet, and face, which have greater concentrations of thermoreceptors, may further optimize the rate at which prewarming therapy may be conducted.

Summary

The maintenance of normothermia during anesthesia and surgery improves clinical outcomes[76]; however, only a fraction of surgical patients receive perioperative warming and, as a result, many surgical patients become hypothermic at some point during their surgical intervention. Most of the hypothermia observed within the first hour following induction with anesthesia is the result of a primarily adiabatic redistribution of heat within the body and is not amenable to any form of externally applied heat. The improvement of surgical instruments and technique has led to a steady decline in operative time that has rendered intraoperative warming during the first hour after anesthetic induction a relatively ineffective therapy since redistribution tends to increase the peripheral cutaneous temperature and reduce the temperature difference between the skin and the warming surface. A commonly cited reason for failing to provide warming is that it interferes with preoperative workflow once the patient is actually in the operating room, especially for outpatient procedures.[77] One solution to this problem is to prewarm the patient prior to arrival in the operating room. Prewarming is also known to improve surgical outcomes[22]. The goal of prewarming is to raise the mean body temperature to its maximum tolerable level as rapidly as possible without provoking a compensatory thermoregulatory response. Current research suggests that thirty minutes of prewarming with existing convective warming blankets provides protection against hypothermia for approximately one hour in most cases. The barriers to prewarming are 1) the additional time spent in the preinduction area and 2) autonomic responses that resist additional heat in the body. Future research should focus on methods to minimize the amount of time required to prewarm patients requiring anesthesia by exploiting high intensity focal warming on areas of the body that are insensitive to the rate of temperature change.

The following table lists several advantages and disadvantages related to the use of convective prewarming.

Advantages	Disadvantages
Inexpensive	Interferes with current workflow practices
Safe	Current therapy adds at least 30 minutes of presurgical time
Can be used when intraoperative warming is contraindicated (aortic cross clamp, orthopedic cases)	Interferes with preoperative access to the patient
Permits unrestricted intraoperative patient access	Adds minor costs to short-duration surgery
Does not contaminate sterile field	Ineffective if patient begins to sweat
Does not interfere with OR equipment	
Generally well-tolerated and comfortable	
Effective during at least the first postinduction hour	
Reduces the incidence of surgical site infection	
Reduces the potential for nosocomial transmission of pathogens by eliminating the need for intraoperative warming	
Preoperative warming blanket may be used in surgery and PACU	
Sensate patients can control degree of heating	

Table 1 – Advantages and disadvantages of convective prewarming

Risks and Benefits
Other than thermal discomfort during periods where heat is applied for an extended duration, there are no other reported adverse side-effects of convective prewarming. Some volunteers have complained of thermal discomfort and sweating following an hour of vigorous whole-body prewarming. Patients in the treatment group may experience the benefits of surgical normothermia.

Dosage and Treatment Regimen
Subjects assigned to the active treatment group (Bair Paws) will be warmed at the highest temperature setting for at least thirty (30) minutes before the induction of anesthesia. Patients in the control group will be covered with a cotton blanket for at least thirty (30) minutes but will not receive any active warming before induction of anesthesia.

Compliance Statement
This trial will be conducted in compliance with the final protocol, GCP, and all of the applicable regulatory requirements.

Study Population
The subjects for this trial will be drawn from a group of ASA I-II surgical patients presenting for total joint replacement or colorectal surgery at Forest Hills Hospital.

C. Trial Objectives and Purpose
The primary objective of this trial is to confirm whether the Bair Paws gown transfers adequate energy to patients to prevent redistribution hypothermia during colorectal and total joint replacement surgery.

D. Trial Design

Summary
This trial is designed to compare postinduction core temperatures in patients who are prewarmed with the Bair Paws gown system to patients in a control group who did not receive any active prewarming.

Inclusion/Exclusion Criteria
Patients will be excluded from this trial if they suffer from clinically significant peripheral vascular disease (ABI < 0.9), fever, skin lesion, reduced left ventricular function (EF < 40%), coronary artery disease, neurological disease, morbid obesity (BMI > 30), diabetes mellitus, thyroid disease, dysautonomia, Cushing's syndrome, coagulopathy, or arterial hypertension.

Detailed Protocol
Fifty subjects will be randomized to either the active prewarming group (n=25) or the standard care group (n=25). Subjects assigned to the active prewarming group will don a Bair Paws gown to which is connected a Model 875 temperature management unit. The warming duct from temperature management unit will be connected to the lower port of the gown, and the temperature control will be set to its highest setting. Subjects assigned to the control group will receive the current standard of care, which consists of a cotton hospital gown and a cotton blanket. Both groups will be exposed to their respective assigned therapies for an equivalent duration, which is approximately 30 minutes. Following anesthetic induction, all patients will receive intraoperative warming with model 635 underbody blankets and a model 750 temperature management unit set to its highest setting. Core temperature from the distal esophagus will be recorded from the induction of anesthesia to the end of surgery at 15 minute intervals.

Induction drugs, fluid management, and hemodynamic monitoring will be standardized and recordded for all patients participating in the trial.

Following surgery, all patients will be warmed in the PACU in compliance with the standard institutional protocol.

E. Selection of Subjects
Patients will be drawn from the surgical population of Forest Hills Hospital. All patients will be ASA I-II.

F. Treatment of Subjects
A copy of the informed consent document may be found in Appendix B of the protocol. (This document is generally produced by the institution conducting the study; attach the document once the study has been commissioned).

1. Document the qualifications and training of the research staff with respect to human participant protections. A free course with certification is available from the National Cancer Institute at http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp.
2. Describe the procedure for managing adverse events.
3. Describe the procedure for monitoring patient compliance.
4. Describe the medication(s)/treatment(s) permitted and not permitted before and/or during the trial.

G. Assessment of Efficacy
Core temperature will be recorded at induction and every 15 minutes following the induction of anesthesia until the patient leaves the operating room. Efficacy will be assessed by comparing the mean core temperature of the treatment group to the corresponding mean from the control group.

H. Assessment of Safety
The Bair Paws warming system is a fully released medical product that has undergone extensive safety evaluation. The warming system will be used according to its labeling; therefore, no additional safety analysis needs to be performed.

I. Power and Statistical Analysis of Data
Time-dependent temperature data will be evaluated using repeated-measure ANOVA with a Greenhouse-Giesser correction for sphericity. Results will be expressed as mean ± SD. The experimentwise error rate is $\alpha = 0.05$. Differences between the two treatment groups will be compared with an unpaired, two-tailed Student's t test. Data will be presented as means ± SD.

A repeated measures design with 1 between factor and 1 within factor has 2 groups with 21 subjects each for a total of 42 subjects. Each subject is measured 15 times. This design achieves 81% power to test factor B if a Geisser-Greenhouse Corrected F Test is used with a 5% significance level and the actual effect standard deviation is 1.00 (an effect size of 0.45), achieves 100% power to test factor W if a Geisser-Greenhouse Corrected F Test is used with a 5% significance level and the actual effect standard deviation is 1.60 (an effect size of 1.80), and achieves 100% power to test the BW interaction if a Geisser-Greenhouse Corrected F Test is used with a 5% significance level and the actual effect standard deviation is 1.60 (an effect size of 1.80).[78]

J. Direct Access to Source Data/Documents
The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by the sponsor by providing direct access to the source data/documents.

K. Quality Control and Quality Assurance
The principles of GCP will be followed; CRFs will be audited and properly corrected if errors are found, and that the suggestions and findings of the trial monitors will be acted on in good faith.

L. Ethics

M. Data Handling and Record Keeping
Describe all of the procedures for data entry and validation, data retrieval, database management, security and storage of trial records, rules for handling noncompliant subjects, determining evaluable data, DSMB records, source data verification, audit, record retention policy, and compliance with any data protection laws.

Decide whether to register the trial at http://.www.ClinicalTrials.gov.

N. Financing and Insurance
Describe the arrangements made to make payment for the conduct of the trial. EU Clinical Trials Directive requires coverage for both nonnegligent and negligent harm.

O. Publication Policy
Describe in detail the policy agreed to in the Investigator's agreement concerning the publication of the trial-related information.

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